HSIA
halogenated solvents industry alliance, inc.

October 17, 2017

EPA Docket Center (ORD Docket)
Mail Code 28221T
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket ID EPA-HQ-ORD-2017-0497

Dear Sirs:

EPA recently solicited comment on draft IRIS Assessment Plans (IAPs) for ethylbenzene, nitrate/nitrite, and chloroform. 82 Fed. Reg. 43539 (Sept. 18, 2017). The Halogenated Solvents Industry Alliance, Inc. (HSIA) offers these comments directed primarily at the IAP for chloroform, which is manufactured by some HSIA members.

1. Selection process for chloroform as the subject of an IRIS reassessment lacks transparency.

In December 2015, EPA published the IRIS Program multi-year agenda providing information to the public on (i) IRIS assessments currently underway and their status and (ii) prioritization of assessments to be initiated over the next few years.[1] As stated in the publication, "the top priority chemical assessments are those with the highest potential public health impacts and/or exposure and would be useful in anticipated EPA decision-making." Some 22 chemicals or groups of chemicals are on the list of chemicals currently being assessed, while 15 others, shown in the following table, are "identified as having the highest priority for assessment" over the next few years.

Groups of chemical assessments in priority order

Group	Chemicals
1	Manganese Mercury Methylmercury Nitrate and nitrite Perfluoroalkyl compounds Vanadium and compounds
2	Acetaldehyde Ammonia (oral) Cadmium and compounds Uranium (effects not associated with radioactivity)

[1] https://www.epa.gov/iris/iris-agenda

3	Di-(2-ethylhexyl) phthalate Dichlorobenzene isomers Methyl t-butyl ether (MTBE) Nickel and compounds Styrene

Source: Table 2 from IRIS Program Multi-Year Agenda (December 2015)

Of the three chemicals or groups of chemicals for which draft IAPs have been developed, ethylbenzene is listed in the 2015 publication as currently under assessment while nitrate and nitrite are listed as a priority in the above table. Chloroform does not appear on either list.

Although the 2015 publication does mention "[d]eveloping a process to update and maintain finalized IRIS assessments that do not warrant a full reassessment through the IRIS process," no details on the prioritization process leading to the selection of chloroform are provided in the draft IAP or on the IRIS website. The chloroform IAP does indicate that there was interest in derivation of an RfC from some EPA program and regional offices, however, specific details were lacking. If, in fact, transparency is a goal of the IRIS Program, EPA needs to provide further information on the selection/prioritization process as well as providing an update of the 2015 multi-year agenda.

2. While the process used to select chemicals for reassessment needs to be more transparent, EPA's apparent willingness to update specific toxicity criteria is encouraging.

Although, as discussed above, the rationale for targeting chloroform for reassessment has not been provided, EPA's apparent willingness to focus attention on a single toxicity criterion (*i.e.*, the reference concentration or RfC), without conducting a complete IRIS assessment, should enable the Agency quickly and cost-effectively to integrate relevant new scientific information into the IRIS process. One criticism of the current IRIS Program is that, for data-rich chemicals, the time required to finalize a full IRIS assessment almost ensures that the assessment will not be current. The ability selectively to develop a missing toxicity factor, as in the case of chloroform, or to reassess an existing factor based on new toxicity information must be viewed as a positive step.

3. Although integration of systematic review into the IRIS assessment process appears to be a positive step, more information on the specifics of the approach needs to be provided.

In its recent presentation to the Science Advisory Board's Chemical Assessment Advisory Committee, EPA provided a fairly intensive description of systematic review and its potential integration into the IRIS program. Formalizing/standardizing the search and selection process for relevant scientific data is a positive step, but until specifics are provided it is difficult to provide anything other than encouragement. The recently finalized rule for conducting risk evaluations under the Lautenberg Chemical Safety Act (LCSA) embraced a number of principles

that we feel should also be key components of the 'new' IRIS approach. Although consideration of the 'best available science' has not always been demonstrated in existing IRIS assessments, it should certainly be embraced in any systematic review approach. Equally important is a 'weight of evidence' approach in the evaluation of any scientific data identified through a systematic review paradigm. The recent EPA slide presentation to the Chemical Assessment Advisory Committee focused heavily on the mechanics of designing and conducting a systematic review, but decisions on 'best available science' and 'weight of evidence' will have to involve human judgment and it is unclear at this time how this will be achieved. Study quality is an additional key element that plays a critical role in supporting 'best available science' and application of 'weight of evidence.' Evaluation of study quality and subsequent application of that information in a determination of which studies are considered sufficiently high quality to support 'best available science' and 'weight of evidence' assessments represent critical aspects of a systematic review that need to be detailed and followed.

4. EPA's integration of chloroform's mode of action (MOA) into its IRIS strategy is positive and should be emulated in the assessment/reassessment of other chemicals.

One of the frequent criticisms leveled at the 'old' IRIS was the Agency's reluctance to acknowledge that the production of cancer in mammals following chemical exposure could exhibit a 'threshold' below which cancer would not develop. An MOA analysis, conducted in 2001, concluded that chloroform is likely carcinogenic by all routes of exposure but *only* under high-exposure conditions which lead to cytotoxicity and regenerative hyperplasia. At exposure levels below this 'threshold' there will be no cytotoxicity and thus no cancer. Acceptance of this concept by the Agency represents a breakthrough which should be applauded. As chloroform is not the only chemical where cancer in animals is associated with cytotoxicity and regenerative hyperplasia, EPA's acknowledgement of a 'threshold' in the dose-response relationship could revolutionize how these chemicals are handled within the IRIS program.

5. EPA's strategy for managing potential cancer risks in the chloroform IAP acknowledges the fallacy of the default linear low-dose extrapolation approach and should be supported.

In the background section of the chloroform IAP, EPA acknowledges that the inhalation unit risk (IUR) posted in 1987 "incorporated a linear extrapolation approach for dose-response that implicitly assumes a risk of cancer at all nonzero exposures." As described in the previous comment, that approach fails to acknowledge the existence of a 'threshold' as demonstrated in the 2001 MOA analysis. Linear low-dose extrapolation has historically been the default approach within the IRIS program and has been criticized by many in the scientific community. EPA's acknowledgement that such an approach represents a shortcoming in the existing IRIS assessment for chloroform also represents a breakthrough and the Agency should be applauded for taking that position and be encouraged to move away from application of linear low-dose

extrapolation as its default position. Indeed, understanding a chemical's mode of carcinogenic action forms the scientific basis for the selection of the dose-response extrapolation method that best aligns with the underlying biology of the specific MOA pathway, and subsequently, ensures that the best available science is used for quantifying potential cancer (or non-cancer) risks at environmental levels of exposures. This approach is codified in the 2005 EPA guidelines on cancer risk assessment.[2]

Given the improved understanding of basic biological functions and the importance of the WHO/IPCS MOA framework[3,4] in toxicology today, this kind of approach should be the default. Indeed, a recent publication[5] describes an advanced approach for quantitative confidence scoring to compare alternative MOAs to determine and communicate the most likely operative MOA based on the weight of scientific evidence. This method provides a scientifically based weight of evidence approach for selecting the most appropriate extrapolation method for determining potential human health risks, including cancer. In fact, this approach should prove to be useful not only for chloroform but for all assessments that deal with potential carcinogenic (or non-carcinogenic) risks, especially where alternative (non-mutagenic) MOAs with supporting mechanistic data are credible.

In Section 3 of the IAP, EPA states that the objective of the assessment is to derive an RfC for chloroform and that, if the newly-derived RfC is protective with respect to cancer, the existing IUR will be withdrawn. If the RfC is not protective for cancer, "the available inhalation data will be evaluated to determine whether they can be used to derive a revised IUR." Given the MOA implications discussed above, which invalidate the use of a linear low-dose extrapolation approach supporting the current IUR, application of MOA to derive a new IUR for chloroform should result in a science-based and thus more defensible IUR value. However, EPA

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[2] Environmental Protection Agency, Risk Assessment Forum. Guidelines for carcinogen risk assessment (EPA/630/P-03/001F) (2005). http://www.epa.gov/cancerguidelines/.

[3] Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. J. Appl. Toxicol. 34: 1–18.

[4] Meek ME, Palermo CM, Bachman AN, North CN, and Lewis RJ. 2014. Mode of action human relevance (species concordance) framework: Evolution of the Bradford Hill considerations and comparative analysis of weight of evidence. J. Appl. Toxicol. 34: 595–606.

[5] Becker RA et al., 2017. Quantitative weight of evidence to assess confidence in potential modes of action. Regul Toxicol Pharmacol. 86: 205-220. OPEN ACCESS: http://www.sciencedirect.com/science/article/pii/S0273230017300387?via%3Dihub.

would have to identify a scientifically-acceptable methodology for calculation of an IUR that is not based on linear no-threshold risk models.

6. To ensure transparency in the 'new' IRIS approach, HSIA encourages EPA to seek and consider stakeholder input throughout the entire assessment process.

As indicated by the draft IAPs released for ethylbenzene, nitrate/nitrite, and chloroform, the 'new' IRIS approach represents a sea change from the approach used previously and it is important that stakeholder input be sought, considered, and incorporated as appropriate. EPA's September 2017 presentation to the Science Advisory Board's Chemical Assessment Advisory Committee is acknowledged, however it is also important that the Committee's response to the briefing as well as EPA's response to any recommendations from the Committee be shared with the public and other stakeholders. Given the widespread use of IRIS toxicity values in the estimation of chemical risk and their role in driving risk management decisions, we would hope that EPA would seek and consider feedback from other Federal and State agencies, as well as from the public, as the Agency moves forward with modifications to the IRIS Program.

Respectfully submitted,

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